CLAIMS

1. Process for the preparation of stable activated derivatives of carbamic acid, comprising at least one protected amino group and an activated carbamic acid function, from an amino acid derivative in which the amino group is protected, comprising:

a) a step of transformation of the -COOH group of the amino acid derivative into a $-CON_3$ group to obtain an acyl azide,

b) a step of transformation of the $-CON_3$ group of the acyl azide into a -NCO group to obtain an isocyanate,

c) a step of treating the isocyanate to obtain said stable derivative of carbamic acid.

2. Process according to claim 1, in which the structure of the carbamic acid derivative is conferred by a group from a compound selected from: N-hydroxysuccinimide, phenol, pentafluorophenol, pentachlorophenol, p-nitrophenol, 2,4-dinitrophenol, 2,4,5-trichlorophenol, 2,4-dichloro-6-nitrophenol, hydroxy-1,2,3-benzotriazole, 1-oxo-2-hydroxydihydrobenzotriazine (HODhbt), 7-aza-1-hydroxy-benzotriazole (HOAt), 4-aza-1-hydroxybenzotriazole (4-HOAt), imidazole and tetrazole.

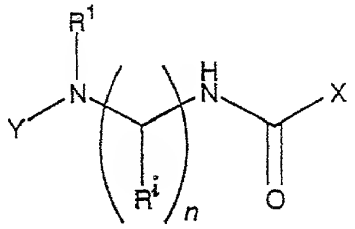
3. Process according to claim 1 or 2, in which the structure of the activated derivative of carbamic acid is conferred by the N-hydroxysuccinimide group.

4. Process for preparation according to claim 1, in which step a) of transformation of the -COOH group to a $-CON_3$ group is carried out by treatment, with the nitride ion, of an activated derivative of the amino acid in which the amino group is protected.

5. Process for preparation according to claim 1, in which step a) of the transformation of the -COOH group into a $-CON_3$ group is carried out by treatment, with hydrazine, of an activated derivative of the amino acid in which the amino group is protected to obtain a hydrazide, which is then converted to a nitrite.

6. Process for preparation according to claim 4, in which step a) of transformation of the -COOH group into a $-CON_3$ group is carried out by treatment of the mixed anhydride (formed from the amino acid derivative) with sodium azide.

7. Compounds of the formula (III bis)



(III bis)

in which

- "n" is a whole number greater than or equal to 1,
- "i" is a whole number varying from 2 to n+1,

- the Y group can be or contain:

1/ a pseudopeptide

2/ an amino acid residue or a chain of amino acids comprising 1 to 10 residues,

3/ a GP group which can be:

- a protective group selected from: a hydrogen atom, an oxycarbonyl (ROCO), acyl, alkyl, aryl, urea, phthalimide (with $R^1 = \emptyset$), biotin, O_2 (with $R^1 = \emptyset$) group,

- or such that the "GP-N" entity forms an "NH_2^+" entity,

- the groups R^1 and R^i can each represent independently from each other: a hydrogen, a halogen, the protected or unprotected side chain of an amino acid selected from natural and synthetic amino acids, a (C1-C20) alkyl group substituted or not, an alkyl group whose cyclic structure contains 5 to 20 carbon atoms, a group OR_a, NH_2, OH, $-COOR_a$, $-CONHR_a$, $-CONH_2$, $-CH_2COOR_a$, $-CH_2CONHR_a$, $-CH_2CONH_2$,

R_a representing an allyl, benzyl, t-butyl, fluorenylmethyl, alkyl having 1 to 20 carbon atoms group, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

- the X group represents a group conferring on the compound of formula (III bis) a structure of an activated derivative of carbamic acid, which X group is from a compound selected particularly from phenols, if desired substituted with at least one nitro or at least one halogen, or hydroxylamine derivatives, or hydroxy-1,2,3-benzotriazole, 1-oxo-2-hydroxydihydrobenzotriazine (HODhbt), 7-aza-1-hydroxy-benzotriazole (HOAt), 4-aza-1-hydroxybenzotriazole (4-HOAt), imidazole and tetrazole,

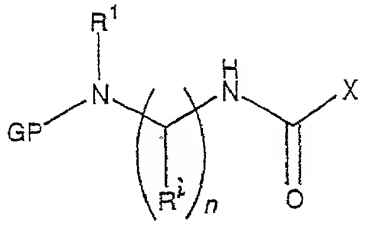
- the R^1 and R^i groups can also form a cycle,

provided that the compound of formula (III bis) is different from the following compounds in which:

- n=2, GP=Boc, R^1=isobutyl, R^2=R^3=H, X=4-nitrophenol
- n=2, GP=Boc, R^1=benzyl, R^2=R^3=H, X=4-nitrophenol
- n=2, GP=Boc, R^1=CH_2-p-C_6H_4Ot-Bu, R^2=R^3=H, X=4-nitrophenol
- n=2, GP=Boc, R^1=H, R^2=R^3=H, X=4-nitrophenol

8. Compounds according to claim 7, in which the X group is from a compound selected from: N-hydroxysuccinimide, pentafluorophenol, p-nitrophenol and imidazole.

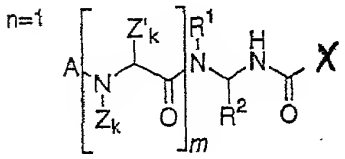
9. Compounds according to claim 7 or 8, having the formula (I bis)

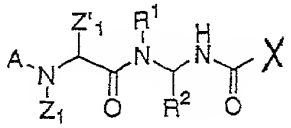


(I bis)

in which n, i, GP, X, R^1 and R^i have the meanings given in claims 7 or 8.

10. Compounds according to claim 7 or 8, having the following formulas:





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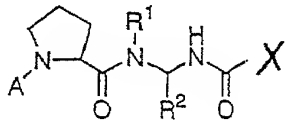

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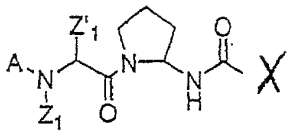

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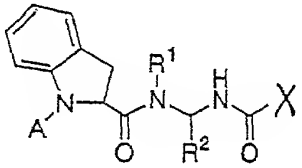

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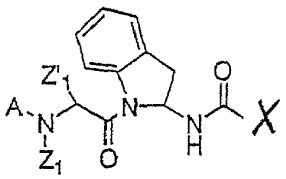

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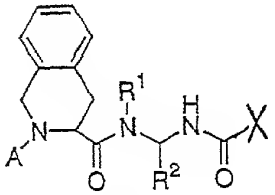

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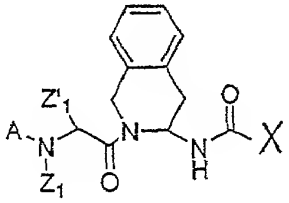

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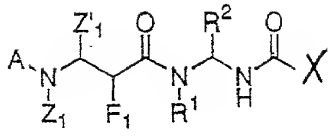
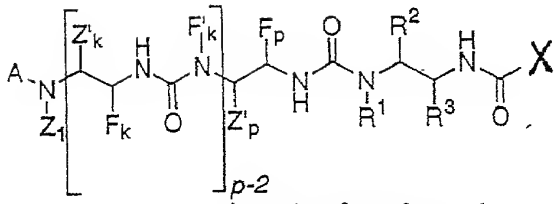
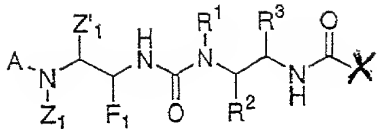


n=2

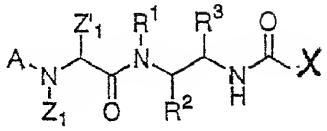


p-2

k varying from 2 to p-1



p=1



in which

- m and p are comprised from 1 to 10,

- A represents either a protective group selected from the following groups: a hydrogen atom, an oxycarbonyl (ROCO), acyl, alkyl, aryl, urea, phthalimide (with R^1 = Ø), biotin group, or the group A can form with the nitrogen atom with which it is contiguous an "NH_2^+" entity,

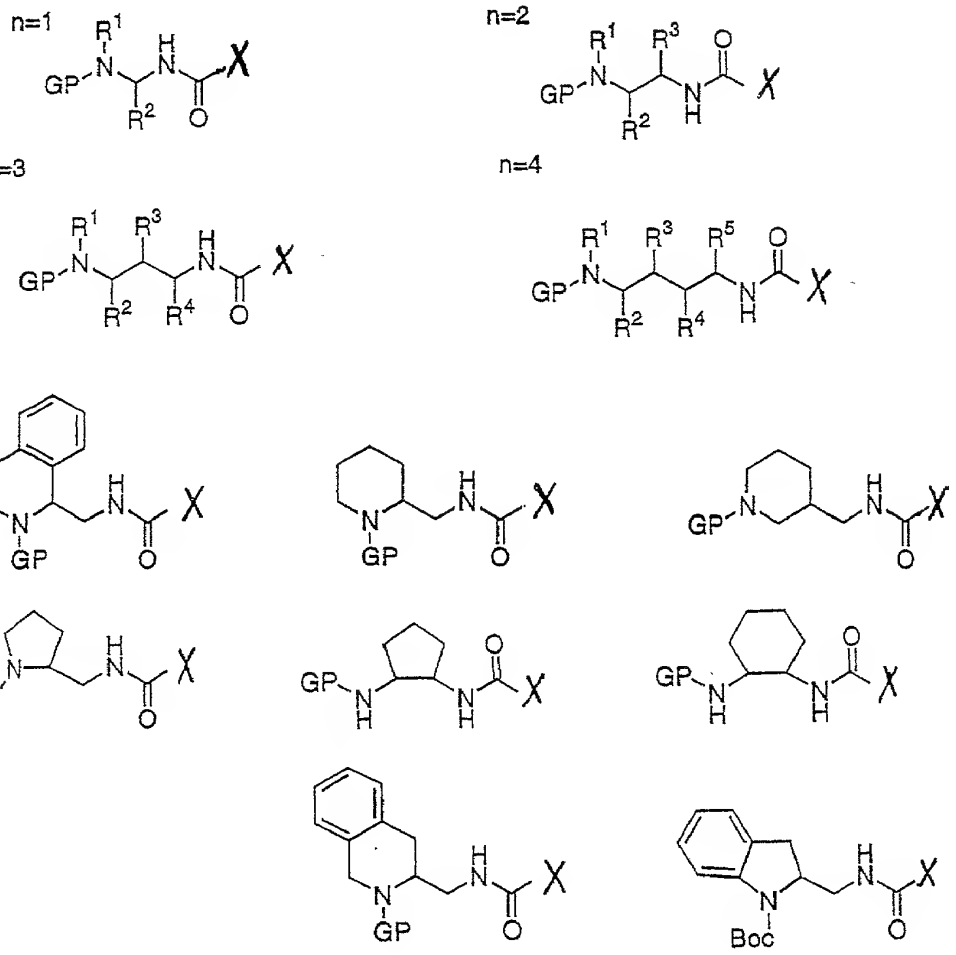
- Z_k, Z'_k, F_k and F'_k represent independently of each other a hydrogen atom, a protected or unprotected side chain of an amino acid selected from natural and synthetic amino acids, a halogen, a (C1-C20) alkyl group, substituted or not, or an aryl group.

11. Compounds according to claim 10, in which X represents the N-hydroxysuccinimide group.

12. Compounds according to claim 9, having the formula (Ibis) in which $1 \leq n \leq 4$, X is as defined in claim 7 and is particularly from p-nitrophenol, N-hydroxysuccinimide, pentafluorophenol, hydroxy-1,2,3-benzotriazole or

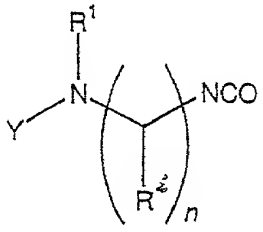
imidazole, GP is an oxycarbonyl group or acyl group as defined in claim 7.

13. Compounds according to claim 12, having the following formulas:



14. Compounds according to claim 13, in which X represents the N-hydroxysuccinimide group.

15. Compounds of the formula (IV)



(IV)

in which

- "n" is a whole number greater than or equal to 1,
- "i" is a whole number varying from 2 to n+1,

- the Y group can be or contain:

1/ a pseudopeptide

2/ an amino acid residue or a chain of amino acids comprising 1 to 10 residues

3/ a GP which can be:

- a protective group selected from: a hydrogen atom, an oxycarbonyl (ROCO), acyl, alkyl, aryl, urea, phthalimide (with R^1 = Ø), biotin, O_2 (with R^1 = Ø) group,
- or such that the "GP-N" entity forms an "NH_2^+" entity,

- the groups R^1 and R^i can each represent independently from each other: hydrogen, halogen, protected or unprotected side chain of an amino acid selected from natural or synthetic amino acids, a (C1-C20) alkyl group substituted or not, an aryl group, whose cyclic structure contains 5 to 20 carbon atoms, an OR_a, NH_2, OH, $-COOR_a$, $-CONHR_a$, $-CONH_2$, $-CH_2COOR_a$, $-CH_2CONHR_a$, $-CH_2CONH_2$ group,

R_a representing an allyl, benzyl, t-butyl, fluorenylmethyl, alkyl having 1 to 20 carbon atoms group, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

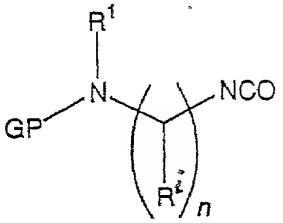
- the groups R^1 and R^i can also form a cycle,

provided that the compound of formula (IV) is different from the compounds in which:

- n=1, GP=Boc or benzyloxycarbonyle, R_1=Ø
- n=2, GP=phtalimide, R_1=Ø, R_3=benzyle, R_2=H
- n=2, GP=phtalimide, R_1=Ø, R_3=methyle, R_2=H
- n=2, GP=phtalimide, R_1=Ø, R_3=H, R_2=H
- n=2, GP=phtalimide, R_1=Ø, R_3=CH_2i-Pr, R_2=H

- n=2, GP=phtalimide, R_1=Ø, R_3=CH_2COOt-Bu, R_2=H
- n=2, GP=phtalimide, R_1=Ø, R_3=CH_2 CH_2 CH_2 CH_2NHBoc, R_2=H
- n=2, GP=phtalimide, R_1=Ø, R_3=$CH_2CH_2CH_2NHCNH$(N-Mtr), R_2=H, (Mtr=4-methoxy-2,3,6-trimethyl-benzenesulphonyle)
- n=2, GP=Boc, R_1=benzyle, R_2=R_3=H
- n=2, GP=Boc, R_1=*i*-Bu, R_2=R_3=H
- n=2, GP=Boc, R_1=H, R_2=R_3=H

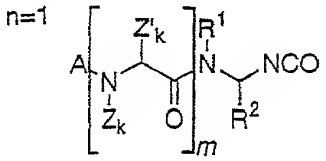
16. Compounds according to claim 15, having the formula (II):

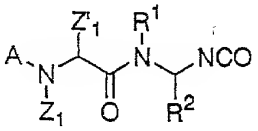


(II)

in which n, i, GP, R^1 and R^i have meanings mentioned in claim 15.

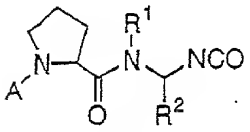
17. Compounds according to claim 15, having the following formulas:



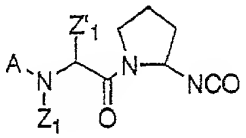


m =1

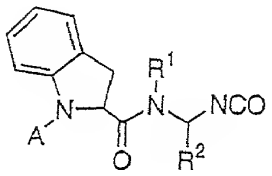
A different from Boc (tertbutoxycarbonyle) and benzyloxycarbonyle



m =1



m =1



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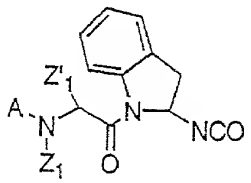

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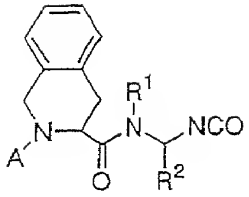

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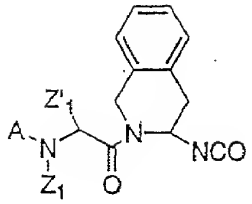

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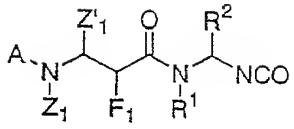
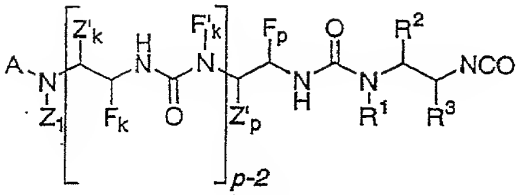
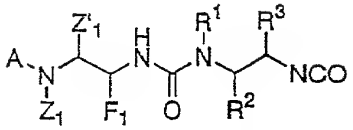


n=2

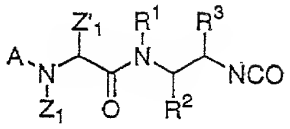


p-2

k varying from 2 to p-1



p=1



in which

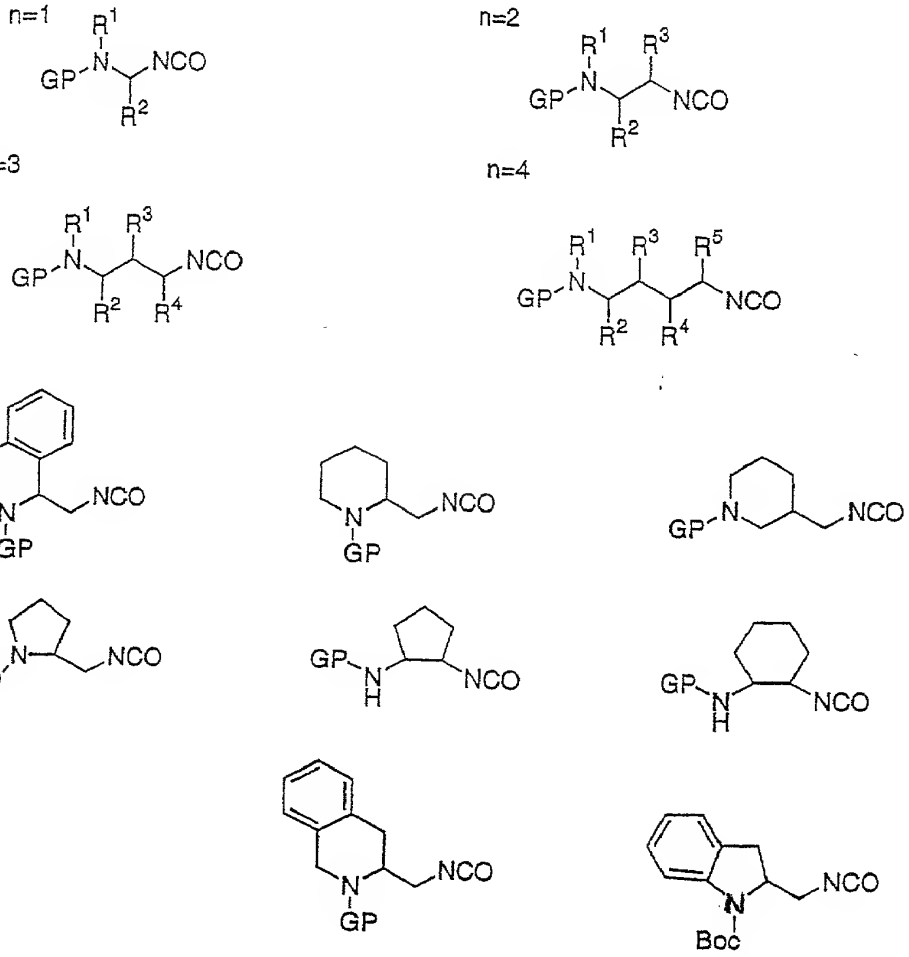
- m and p are comprised from 1 to 10,

- A represents either a protective group selected from the following groups: a hydrogen atom, an oxycarbonyl (ROCO), acyl, alkyl, aryl, urea, phthalimide (with R^1 = Ø), biotin group, or the group A can form with the nitrogen atom with which it is contiguous an "NH_2^+" entity,

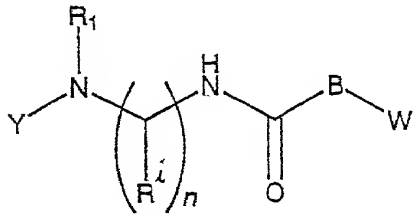
- Z_k, Z'_k, F_k and F'_k represent independently from each other a hydrogen atom, a protected or unprotected side chain of an amino acid selected from natural and synthetic amino acids, a halogen, a (C1-C20) alkyl group, substituted or not, or an aryl group.

18. Compounds according to claim 16, having the formula (II) in which $1 \leq n \leq 4$, GP is an oxycarbonyl group or acyl

group such as defined in claim 15, and particularly the following compounds, in particular those for which GP = Boc and Fmoc:



19. Compounds of formula (VII)



(VII)

in which

- "n" is a whole number greater than or equal to 1,
- "i" is a whole number varying from 2 to n+1,

- the Y group can be or contain:

1/ a pseudopeptide

2/ an amino acid residue or a chain of amino acids comprising 1 to 10 residues

3/ a GP group which can be:

- a protective group selected from: oxycarbonyl (ROCO), acyl, alkyl, aryl, urea, phthalimide (with R^1 = Ø), biotin, O_2 (with R^1 = Ø),

- or such that the "GP-N" entity forms an "NH_2^+" entity,

- the groups R^1 and R^i can each represent independently of each other: hydrogen, halogen, the protected or unprotected side chain of an amino acid selected from natural and synthetic amino acids, a (C1-C20) alkyl group, substituted or not, an aryl group, whose cyclic structure contains 5 to 20 carbon atoms, an OR_a, NH_2, OH, $-COOR_a$, $-CONHR_a$, $-CONH_2$, $-CH_2COOR_a$, $-CH_2CONHR_a$, $-CH_2CONH_2$ group,

R_a represents an allyl, benzyl, t-butyl, fluorenylmethyl, alkyl group having 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

- the group B can be either N-W' or O,

- the groups W and W' can be or contain:

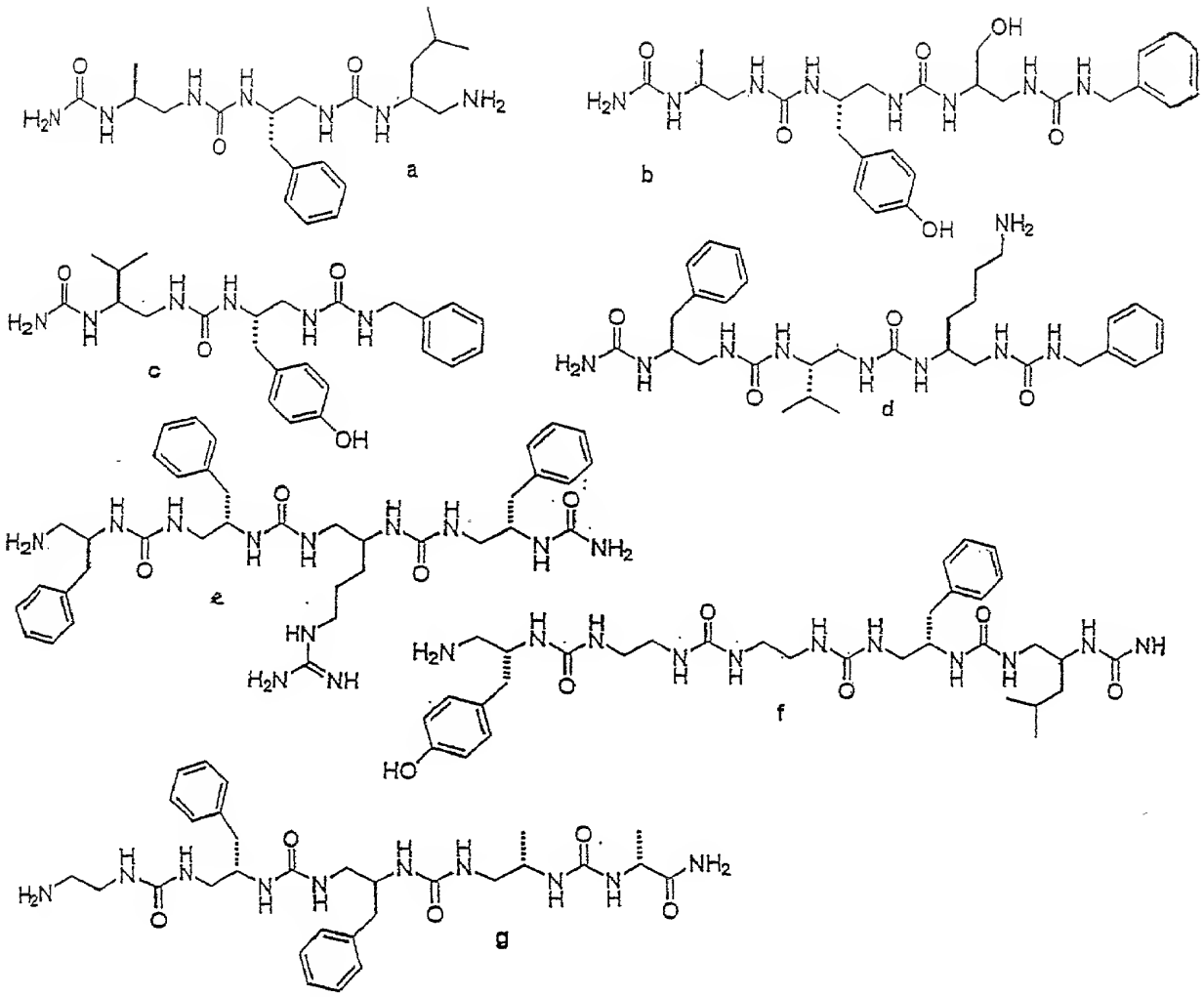
A/ hydrogen

B/ a pseudopeptide

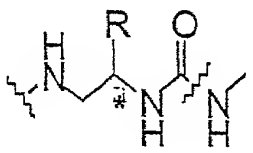
C/ an amino acid residue or a chain of amino acid residues comprising 1 to 10 residues

- the groups R^1 and R^i can also form a cycle,

provided that the compounds of the following formulas are excluded:

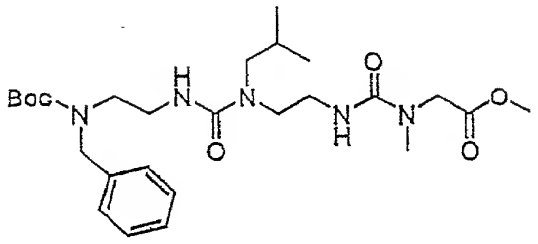


provided that the compound of formula (VII) is different from the analogs of the peptide Tyr-Gly-Gly-Phe-Leu-OH, containing one or several derivatives as defined below mimicking the side chain of amino acids present in the peptide and permitting the introduction of one or several urea linkages, which is to say that the compound of formula (VII) is different from the following compounds:

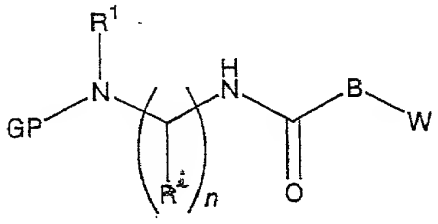


in which R represents hydroxybenzyl, a hydrogen atom, a benzyl group, or an isobutyl group,

and provided that the compound of formula (VII) is different from:



20. Compounds according to claim 19, having the formula (VI):

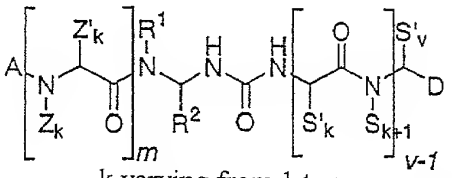


(VI)

in which n, i, GP, R^1, R^i, B and W have the meanings mentioned in claim 19.

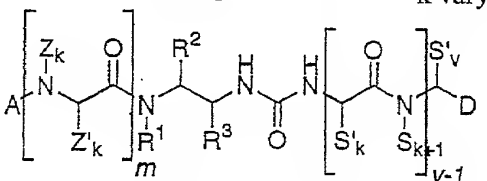
21. Compounds according to claim 19, having the following formulas:

n=1

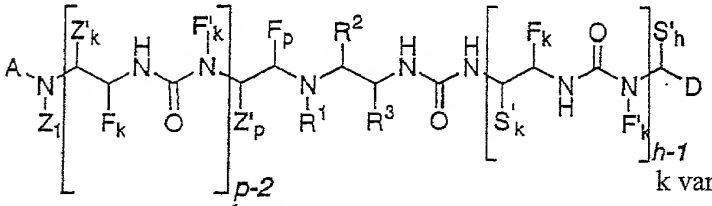


k varying from 1 to m k varying from 1 to v-1

n=2

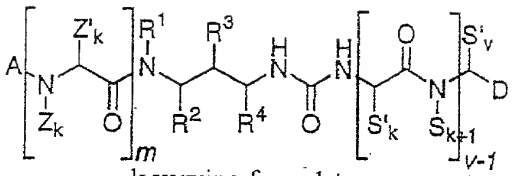


k varying from 1 to m k varying from 1 to v-1



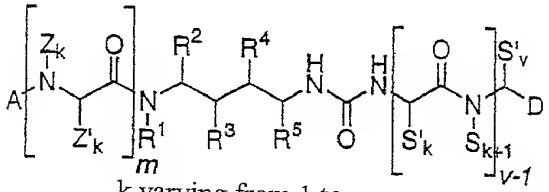
k varying from 2 to p-1 k varying from 1 to h-1

n=3



k varying from 1 to m k varying from 1 to v-1

n=4



k varying from 1 to m k varying from 1 to v-1

in which

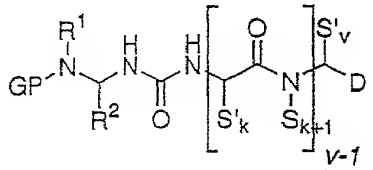
- v and m are comprised from 1 to 10,

- A represents either a protective group selected from the following groups: a hydrogen atom, an oxycarbonyl (ROCO), acyl, alkyl, aryl, urea, phthalimide (with $R^1 = \emptyset$), biotin group, or the group A can form with the nitrogen atom with which it is contiguous an "NH_2^+" entity,

- Z_k, Z'_k, S_k, S'_k and S'_v represent independently from each other a hydrogen atom, a protected or unprotected side chain of an amino acid selected from natural and synthetic amino acids, a halogen, a (C1-C20) alkyl group, substituted or not, or an aryl group.

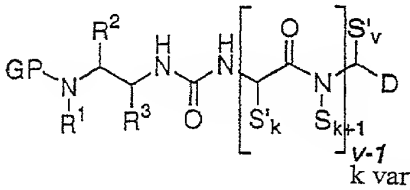
22. Compounds according to claim 20 having the following formulas:

n=1

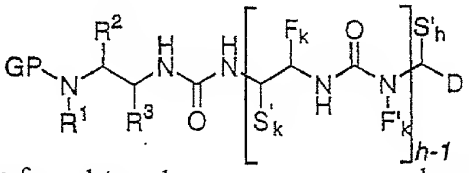


k varying from 1 to v-1

n=2

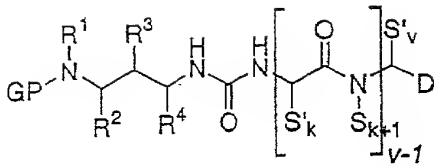


k varying from 1 to v-1



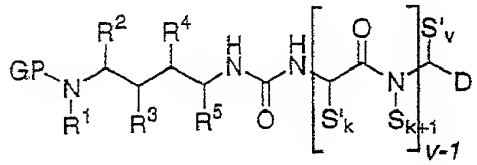
k varying from 1 to h-1

n=3



varying from 1 to v-1

n=4



varying from 1 to v-1

in which

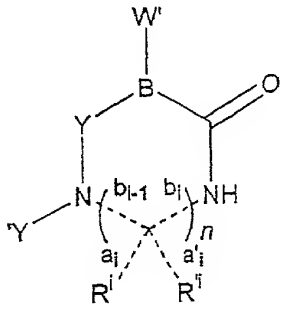
- v and h are comprised from 1 to 10,

- D can represent a hydrogen atom, a -COOH, -$COOR_c$, -$CONH_2$, -$CONR_cR_d$ group,

R_c and R_d representing an allyl, benzyl, t-butyl, fluorenylmethyl, alkyl group having 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

- F_k, F'_k, S_k, S'_k, S'_v and S'_h represent independently from each other a hydrogen atom, a halogen, the protected or unprotected side chain of an amino acid selected from natural and synthetic amino acids, a (C1-C20) alkyl group, substituted or not, or an aryl group.

23. Compounds of formula (VIII)



(VIII)

in which

- W' can be or contain:

A/ hydrogen,

B/ a (C1-C20) alkyl group, substituted or not,

C/ an aryl group, whose cyclic structure contains 5 to 20 carbon atoms,

D/ a protected or unprotected side chain of amino acids selected from proteinogenic and non-proteinogenic amino acids and in the case of proline, W' = $-CH_2-CH_2-CH_2-CH(COOR)-$,

E/ an amino acid residue or a chain of amino acid residues comprising 1 to 10 residues,

- R^i and R'^i represent independently of each other a hydrogen atom, a halogen, the protected or unprotected side chain of an amino acid selected from natural and synthetic amino acids, a (C1-C20) alkyl group, substituted or not, or an aryl group,

- B is a nitrogen atom or an oxygen atom,

- a_i, a'_i, b_{i-1} and b_i represent interatomic bonds that can be single or double,

- the group Y' can be or contain:

I/ a (C1-C20) alkyl group, substituted or not,

II/ an aryl group

III/ a pseudopeptide

- the Y group can be or contain:

I/ a (C1-C20) alkyl group, substituted or not

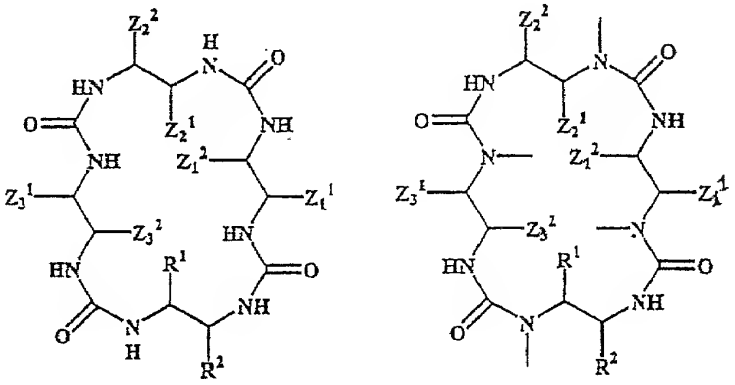
II/ an aryl group

III/ a pseudopeptide

IV/ or form with B an amino acid residue or a chain of amino acid residues comprising 1 to 10 residues, the acid function of the amino acid residue or of the chain of amino acid residues being fixed on the group NY',

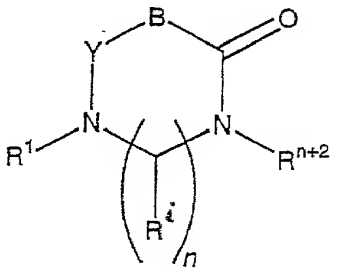
V/ or form with B a urea oligomer comprising 1 to 10 residues, the carbonyl function of the urea residue being fixed on the group NY'.

24. Compounds according to claim 23, having the following formulas:



in which R^1, R^2, Z_1^1, Z_1^2, Z_2^1, Z_2^2, Z_3^1 and Z_3^2 have the meanings indicated for R^i and R'^i in claim 23.

25. Compounds of formula (VIII bis)



(VIII bis)

in which:

- the total number of atoms forming the cycle is greater than six,
- "n" is a whole number greater than or equal to 1,
- "i" is a whole number varying from 2 to n+1,

- the R^1, R^i and R^{n+2} groups can each represent independently of each other: a hydrogen, a halogen, the protected or unprotected side chain of an amino acid selected from natural and synthetic amino acids, a (C1-C20) alkyl group, substituted or not, an aryl group, whose cyclic structure contains 5 to 20 carbon atoms, an OR_a, NH_2, OH, $-COOR_a$, $-CONHR_a$, $-CONH_2$, $-CH_2COOR_a$, $-CH_2CONHR_a$, $-CH_2CONH_2$ group,

R_a representing an allyl, benzyl, t-butyl, fluorenylmethyl, alkyl group having 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

- the groups R^1 and R^i can also form a cycle,

- the group Y can be or contain:

1/ a (C1-C20) alkyl group, substituted or not

II/ an aryl group

III/ a pseudopeptide

IV/ or forming with B an amino acid residue or a chain of amino acid residues comprising 1 to 10 residues, the acid function of the amino acid residue or of the chain of amino acid residues being fixed on the group NR^1,

- the group B can be either N-W' or O,

- the group W' can be or contain:

A/ hydrogen,

B/ a (C1-C20) alkyl group, substituted or not,

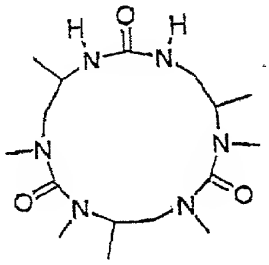
C/ an aryl group, whose cyclic structure contains 5 to 20 carbon atoms,

D/ a protected or unprotected side chain of amino acids selected from proteinogenic and non-proteinogenic amino

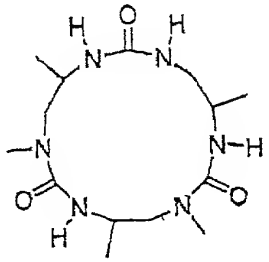
acids and in the case of proline, W' = $-CH_2-CH_2-CH_2-CH(COOR)-$

E/ an amino acid residue or a chain of amino acid residues comprising 1 to 10 residues.

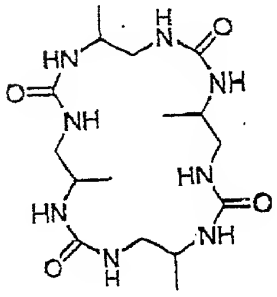
26. Compounds according to claim 23, having the following formulas:



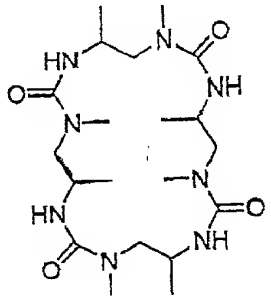
(VIII bis/1)



(VIII bis/2)



(VIII bis/3)



(VIII bis/4)

27. Compounds having one of the formulas (I bis), (II), (III bis), (IV), (VI), (VII) according to one of claims 7 to 22, in which the aryl group can be substituted with 1 to 6 substituents selected from: alkyl, alkoxy, amine, ester, urea, amide, carboxylic acid groups, of 1 to 10 carbon atoms, hydroxyl, nitrile, nitro, guanidine, aryl whose

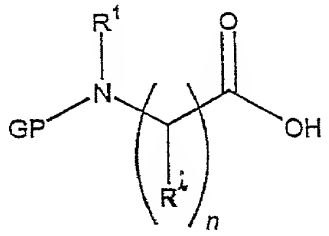
cyclic structure contains 5 to 20 carbon atoms, and a halogen atom.

28. Compounds according to one of claims 7, 15, 19 or 25, in which the alkyl group is substituted with one or several substituents selected from the groups: $-COOR_h$, $-CONHR_h$, -COOH, -OH, $-OR_h$, $-NHR_h$, $-NH_2$, $-NH(CO)R_h$, aryl whose cyclic structure contains 5 to 20 carbon atoms, halogen, carbonyl of 1 to 10 carbon atoms, nitrile, guanidine,

R_h representing an allyl, benzyl, t-butyl, fluorenylmethyl, alkyl group having 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms.

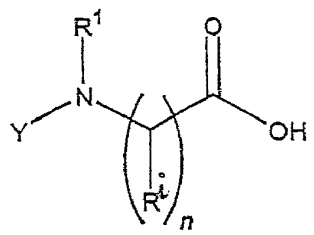
29. Process for preparation according to one of claims 1 to 3, of derivatives corresponding to the formulas (I bis), (II), (III bis) or (IV) according to one of claims 7 to 18, from respectively:

- compounds of formula (IX) (for compounds of formula (I bis) and (II))



(IX)

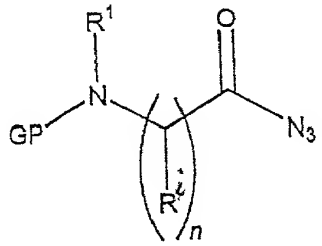
- compounds of formula (X) (for compounds of formula (III bis) and (IV))



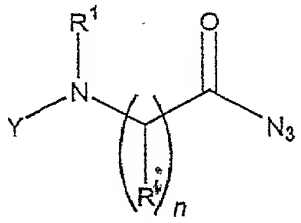
(X)

comprising

(a) a step of transformation of acid (IX) or (X) into the corresponding acyl azide (XII) or (XIII) respectively



(XII)



(XIII)

by a suitable treatment,

(b) a step of transformation of acyl azide (XII) or (XIII) by Curtius rearrangement into the corresponding isocyanate (II) or (IV) respectively,

(c) a step of treatment of isocyanate (II) or (IV), preferably not isolated, under conditions permitting obtaining a carbamic acid derivative of formula (I bis) or (III bis).

30. Process for preparation according to claim 29, in which:

- step (a) of transformation of acid (IX) or (X) into the corresponding acyl azide (XII) or (XIII) respectively, is carried out by treatment of the mixed anhydride (formed by the reaction of acid (IX) or (X) with ethyl or isobutyl chloroformiate in the presence of a tertiary amine such as NMM (N-methylmorpholine), DIEA (di-isopropylethylamine), or

Et_3N in THF (tetrahydrofurane)) with a sodium azide solution,

- step (b) of transformation of acyl azide (XII) or (XIII) into the corresponding isocyanate (II) or (IV), is carried out by heating a solution of acyl azide in a suitable solvent,

- step (c) of treatment of isocyanate (II) or (IV) is carried out, when the isocyanate is in solution, for example in toluene, with one of the derivatives of the following list: N-hydroxysuccinimide, phenol, pentafluorophenol, pentachlorophenol, p-nitrophenol, 2,4-dinitrophenol, 2,4,5-trichlorophenol, 2,4-dichloro-6-nitrophenol, hydroxy-1,2,3-benzotriazole, imidazole, tetrazole, 1-oxo-2-hydroxydihydrobenzotriazine (HODhbt), 7-aza-1-hydroxybenzotriazole (HOAt) and 4-aza-1-hydroxybenzotriazole (4-HOAt), and if desired a base such as pyridine, so as to obtain a carbamic acid derivative of formula (I bis) or (III bis), which is then if desired isolated.

31. Process for preparation according to claim 1, of compounds of formula (VI) or (VII) according to one of claims 19 to 22, comprising the reaction of compounds containing primary or secondary amines or alcohols with one of the products of formula (I bis), (II), (III bis) or (IV) according to one of claims 7 to 18, in a solvent, with or without the addition of an organic or mineral base.

32. Process according to claim 31, in which the solvent is selected from: DMF, H_2O/acetone, THF, dichloromethane or acetonitrile.